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Lipase Catalyzed Kinetic Resolution of Pharmaceutically Useful Chloro Alcohols in Heptane

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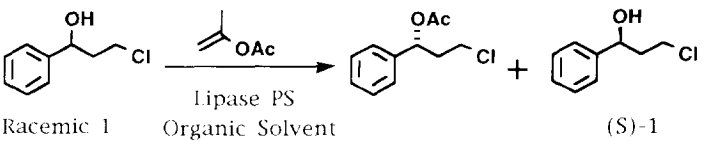
Abstract: Pharmaceutically useful chloro alcohols, 3-chloro-1-phenyl-1-propanol (1), 1-chloro-3-(1-naphthyloxy)-2-propanol (2) and 4-chloro-1-(4-tert-butylphenyl)-1-butanol (3), are prepared in enantiomerically pure form by an efficient lipase PS catalyzed transesterification in heptane. The effect of organic solvent nature on enzyme activity was also studied.

Lipase catalyzed esterifications in organic solvents are a very useful and general method for the resolution of racemic alcohols and acids.[1] The nature of the organic solvent used in the enzymatic reactions shows a profound effect on the stereo and regioselectivities of enzymes.[2] These exceptional properties of the enzymes have been widely used for the synthesis of enantiomerically enriched biologically active molecules.[3] Since the biological activity resides in only one enantiomer of the racemic drug, the homochiral drugs are highly desirable.[4] 3-Chloro-1-phenyl-1-propanol 1 is a useful intermediate in the synthesis of antidepressants Tomoxetine, Fluxetine and Nesoxetine. Compound 1 has been prepared in enantiomercally pure form by the reduction of the corresponding ketone with the chiral catalysts.[5] Schneider et. al have reported the synthesis of (R) and (S)-1 by enzymatic hydrolysis of its chloro acetate in phosphate buffer.[6] The kinetic resolution of 1 using lipases in organic solvents has not been reported. We herein report our results on the kinetic resolution of racemic 1.

Scheme I



Racemic 1 (S)-1

Table 1. Effect of organic solvent on lipase PS catalyzed esterification of racemic 1.[a]

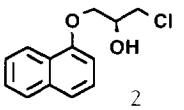
Solvent	Log p	% of Conversion	e.e.[b](Conf.)		E[7]
			Alcohol	Acetate	
Heptane	4.0	54	99 (S)	84 (R)	56
Hexane	3.5	53	98 (S)	84 (R)	42
Toluene	2.5	35	50 (S)	94 (R)	54
Chloroform	2.0	26	33 (S)	94 (R)	45
Isopropyl ether	1.9	39	60 (S)	94 (R)	60
Tetrahydrofuran	0.49	9	9 (S)	99 (R)	219
Acetonitrile	- 0.33	32	94 (S)	96.5 (R)	88

[a] Substrate (0.3 mM), isopropenyl acetate (1.2 mM), organic solvent (1.2 mL) and lipase PS (30 mg) at 37 °C.
[b] Determined by HPLC analysis on chiralcel OD column with 5% isopropanol in hexane as solvent system.

We have performed the transesterification of racemic 1 (Scheme I) with lipase PS (Amano) in different organic solvents whose log p values ranging from 4 to -0.33 with isopropenyl acetate as the acylating agent for 96 hours (Table 1). The low activity of the lipases in hydrophilic solvents may be due to the distribution of essential water arround the biocatalyst.[1]

The stereoselectivity of the lipase PS for racemic 1 is not affected by the nature of organic solvent; it is consistent with the lack of influence of water activity on the enantioselectivity as has been observed previously.[8] The best results were obtained when heptane was used as the solvent. We have applied the same reaction conditions for the resolution of two more pharmaceutically useful chloro alcohols, 1-chloro-3-(1-naphthyloxy)-2-propanol 2,[9] a useful intermediate in the synthesis of β-blocking agent propranolol and 4-chloro-1-(4-tertbutylphenyl)-1-butanol 3,[10] a useful intermediate in the synthesis of antihistamine terfenadine and prepared them in optically pure form. In a typical experiment, to the racemic alcohol (5 mM) in heptane (20 mL), isopropenyl acetate (20 mM) and lipase powder (500 mg) were added and incubated at 37 °C. After appropriate time (Table 2) the lipase powder was filtered, alcohol and acetate were separated by column chromatography. Racemic 2 is not soluble in heptane, but in the presence of isopropenyl acetate at 37 °C, it is soluble and the lipase catalyzed the acylation efficiently. In conclusion, we have prepared three enantiomerically pure chloro alcohols with the distance ranging from two to four carbon between chloro and hydroxy group. These compounds are important intermediates for the synthesis of pharmacutically useful adducts. Our results provide further evidence that the hydrophobicity of the organic solvent enhances the rate of transesterification.[11]

Scheme II



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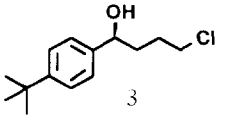

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Table 2: Lipase catalyzed esterification of racemic 1-3 in heptane.

Substrate	Time (hour)	Conv. (%)	Alcohol				Acetate		E[7]
			Yield	e.e.	Conf.[a]	Specific Rotation $[\alpha]_D^{20}$	Yield	e.e.	
1	96	52	44	99[b]	S	-24.7(C=1.44, $CHCl_3$)	49	92.4[b]	152
2	24	52.5	44	99[c]	R	- 8.5(C=5.27, EtOH)	41	89[c]	82
3	96	50	47	99[c]	S	-33.9(C=1.33, $CHCl_3$)	47	99[d]	1059

[a] Determined by comparing the sign of specific rotation of 1, 2 and 3 with reference 6, 9b and 10, respectively.
[b] Determined by HPLC on chiralcel OD column with 5% IPA in hexane as solvent system.
[c] Determined by HPLC using chiralcel OJ column with 5% IPA in hexane as the solvent system.
[d] Determined by HPLC on chiralcel OJ column with 0.5% IPA in hexane as solvent system.

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